22 December 2022
EMA/CMDh/920305/2022

Report from the CMDh meeting held on 13-14 December 2022

CMDh outcome on referral pursuant to Article 107i of Directive 2001/83/EC - Pholcodine-containing medicinal products

On 1 December 2022, the PRAC concluded its review of medicines containing pholcodine, which are used in adults and children to treat non-productive (dry) cough and, in combination with other active substances, for the treatment of symptoms of cold and flu, and recommended the revocation of the EU marketing authorisations for these medicines.

The CMDh, having considered the PRAC assessment report and recommendation, agreed by majority that the marketing authorisations for medicinal products containing pholcodine should be withdrawn.

During the review, the PRAC evaluated all available evidence including the final results of the ALPHO study[1], post-marketing safety data and information submitted by third parties such as healthcare professionals. The available data showed that use of pholcodine in the 12 months before general anaesthesia with neuromuscular blocking agents (NMBA) is a risk factor for developing an anaphylactic reaction (a sudden, severe and life-threatening allergic reaction) to NMBAs.

As it was not possible to identify effective measures to minimise this risk, nor to identify a patient population for whom the benefits of pholcodine outweigh its risks, pholcodine-containing medicines are being withdrawn from the EU market and will therefore no longer be available by prescription or over-the-counter.

Healthcare professionals should consider appropriate treatment alternatives and advise patients to stop taking pholcodine-containing medicines. Healthcare professionals should also check whether patients scheduled to undergo general anaesthesia with NMBAs have used pholcodine in the previous 12 months and remain aware of the risk of anaphylactic reactions in these patients.

As the CMDh position was adopted by majority vote, it will now be sent to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

[1] Companies marketing pholcodine medicines were requested to conduct the ALPHO study following a previous safety review conducted in 2011.

Removal of requirement to provide list of dispatch dates

The CMDh has agreed updates of several CMDh guidance documents to remove the requirement for MAHs to provide a list of dispatch dates (dates of dispatch to the CMS) with the RMS submission. With the mandatory use of CESP for submissions, it was considered that the list of dispatch dates is no longer needed. The review follows an update of the CMDh BPG for the handling of Type II Variations in MRP (Chapter 5) in October, where this change was first agreed. The following CMDh guidance documents have been updated:

- Procedure for automatic validation of MRP for Variations (Chapter 2)
- CMDh BPG for the processing of Type IA Minor Variations (Notifications) in MRP (Chapter 3)
- CMDh BPG for the processing of Type IB Minor Variations (Notifications) in MRP (Chapter 4)
- CMDh BPG for the processing of Grouped Applications in MRP (Chapter 6)
- CMDh BPG on Worksharing (Chapter 7)
- Cover letter for Variation Applications in the MRP
- CMDh Best Practice Guide on the processing of renewals in the MRP/DCP

Other minor changes have been included in the updated documents, as necessary. Chapter 5 has also been further updated to be in line with the other CMDh BPGs.

The updated documents will be published on the CMDh website under "Procedural Guidance > Variations", "Templates > Variations" and "Procedural Guidance > Renewal", respectively.

Call for review for chemically synthesised and biological medicinal products regarding nitrosamine impurities

The CMDh and the EMA agreed an update of the EMA/CMDh Q&A on nitrosamines. The Q&As have been updated to provide guidance on the approach to control the presence of nitrosamines exceeding the acceptable intake (AI) during CAPA implementation. In addition, further clarification is provided on the application of the temporary universal AI of 178 ng/day.

The updated document will be published on the EMA website and will be linked from the CMDh website under "Advice from CMDh > Nitrosamine impurities".

CMDh position paper concerning Applicant's request of submission of multiple applications during ongoing DCPs or inclusion of new CMS or additional strength(s) in an already ongoing DCP

The CMDh agreed an update of the CMDh position paper concerning applicant's request of submission of multiple applications during ongoing DCPs or inclusion of new CMS or additional strength(s) in an already ongoing DCP. With the update, the CMDh provides conditions for the inclusion of new CMS during an ongoing DCP (in case of no on-going multiple/duplicate application with the same CMS), specifically to prevent or solve shortages.

The updated document will be published on the CMDh website under "Procedural Guidance > Application for MA".

Update of Applicant's (Joint) Response Template

The CMDh agreed an update of the applicant's (joint) response template – responses to the question raised by RMS and CMSs. A new section has been added for the applicant to provide information (and to keep the RMS informed) about the changes proposed by the applicant in the manufacturing chain and/or in the submitted GMP documents, including the submission of more recent versions during the further steps of the procedure. The use of the template will become mandatory as of 1 February 2023 for all upcoming responses but can already be used on a voluntary basis before that date.

The updated template will be published on the CMDh website under "Templates > Assessment reports > DCP (AR/Comments)".

Q&As on Active Substance Master File (ASMF)

In June 2022, the CMDh adopted an update of the Q&As on ASMF. The update gives further guidance on the version numbering of ASMFs, how to track them and how they relate to the eCTD sequence.

The Q&As are a joint document with several other groups and all involved parties have now adopted the update. The updated document has therefore been published on the CMDh website under "Questions and Answers".

CMDh positions following PSUSA procedures for nationally authorised products only

The CMDh, having considered the PSURs on the basis of the PRAC recommendations and the PRAC assessment reports, agreed by consensus on the variation of the marketing authorisations of medicinal products containing the following active substance:

- bleomycin
- cefuroxime axetil
- cefuroxime sodium (except for intracameral use)
- fentanyl (transdermal patches, solution for injection - nationally authorised product only)
- ivermectin (systemic use)
- lamivudine / tenofovir disoproxil
- methoxyflurane
- omeprazole
- triptorelin
- vinorelbine

Further information regarding the above mentioned PSUSA procedures, including information on the implementation, will be published on the EMA website.

Outcome of PSUR Follow-up procedures

Methotrexate - DE/H/PSUFU/00002014/202110

The CMDh adopted the outcome of the PSUFU procedure for methotrexate.

Based on the review of data submitted, the CMDh agreed that concerned MAHs should update section 4.6 of the SmPC and the relevant section of the PL of their products in line with the outcome of the PSUFU procedure to amend recommendations for contraception in males.

The summary assessment report will be published on the CMDh website under "Pharmacovigilance > PSUR > PSUR Follow-up procedures".

Election of the chair of the Joint CMDh/CMDv Working Party on Variation Regulation

The CMDh has re-elected Susanne Winterscheid (DE) for a two-year term as chair of the Joint CMDh/CMDv working party on Variation Regulation. The CMDv has re-elected Wiebke Godow (DE) for a two-year term as vice-chair of the working party.

Joint meeting with CMDv

The CMDh held a joint meeting with CMDv in the margins of the December CMDv plenary meeting. The topics discussed included the new veterinary legislation, the EU Pharmaceutical Strategy, applications for fixed-dose combinations and transparency.

EU Worksharing Articles 45 & 46 of the Paediatric Regulation – Public Assessment Reports

The CMDh has agreed a public assessment report for paediatric studies submitted in accordance with Article 46 of the Paediatric Regulation for:

- Augmentin ES Powder for Oral Suspension (amoxicillin & clavulanate)

The public assessment report will be published on the CMDh website under "Paediatric Regulation > Assessment reports".

NEW APPLICATIONS

Mutual Recognition Procedure

Table 1. New applications in Mutual Recognition procedure started in November 2022

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria		
Belgium		2
Bulgaria		2
Croatia		

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Cyprus	1	4
Czech Republic	2	
Denmark		3
Estonia		2
Finland		1
France		1
Germany	2	1
Greece		3
Hungary	2	1
Iceland		
Ireland	1	
Italy		1
Latvia		2
Liechtenstein		
Lithuania		4
Luxembourg		2
Malta		4
Netherlands	3	1
Norway	1	2
Poland		2
Portugal	5	1
Romania		3
Slovak Republic		1
Slovenia		
Spain	1	
Sweden	1	3
United Kingdom (Northern Ireland)		

Decentralised Procedure

Table 2. New applications in Decentralised procedure started in November 2022

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Austria	5	11
Belgium		13
Bulgaria		17
Croatia	2	13
Cyprus		8
Czech Republic	10	19
Denmark	5	13
Estonia	2	18
Finland	2	11
France		20

Member State	Number of times involved in a procedure as RMS	Number of times involved in a procedure as CMS
Germany	17	33
Greece		10
Hungary	6	11
Iceland	11	7
Ireland	7	6
Italy	1	20
Latvia	1	17
Liechtenstein		
Lithuania	1	22
Luxembourg		10
Malta	5	5
Netherlands	13	13
Norway		15
Poland	2	16
Portugal	4	21
Romania	1	14
Slovak Republic		22
Slovenia	1	6
Spain	1	25
Sweden	8	13
United Kingdom (Northern Ireland)		1

Information on the above-mentioned issues can be obtained:

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CMDh Secretariat
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http://www.hma.eu/cmdh.html